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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,957	06/20/2003	Garth Powis	126387.530	6628

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
12/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/600,957	POWIS, GARTH	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/22/2008 has been entered.

Claims 7-40 are currently pending and under consideration.

Priority

After reviewing the Provisional Application, SN: 60/031995, for the disclosure of a drug comprising 2-imidazole disulfide formulated in a suitable dosage and a pharmaceutically acceptable carrier for injection or oral administration, the Examiner has established a priority date of **December 12, 1997** consistent with the filing of PCT/US97/22292. If applicant disagrees with any rejection of claims 7-40 set forth in this office action based on examiner's establishment of a priority date of **December 12, 1997** for the instant claims in application serial number 10/600,957 applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7-40 are rejected under 35 U.S.C. 102(a) as being anticipated by Powis et al . (Anti-Cancer Drugs December of 1996; 7 (Suppl. 3): 121-126, IDS).

Powis et al .teach a composition comprising 1-methylpropyl-2-imidazolyl disulfide formulated for intraperitoneal injection or oral administration with a suitable amount of compound to inhibit tumor growth (page 125, Figure 5 and Table 2). With regards to the suitable amount, the publication teaches that a suitable amount includes, 5 mg/kg, 10 mg/kg, or 15 mg/kg, e.g., 15, 30 or 45 mg/m2 (see Applicants Remarks, page 8 out of 10), for intraperitoneal injection or 250 ppm for oral administration (page 125, Figure 5 and Table 2).

Claims 7-30 remain rejected under 35 U.S.C. 102(b) as being anticipated by Oblong et al. (Cancer Chemotherapy and Pharmacology 1994; 34: 434-438, *IDS, of record*) as evidenced by Chaplan et al. (US 5,849,737, 1998, of record) and Padmanaban (US 20070105945, 2007, of record).

Oblong et al. teach a composition comprising an agent in DMSO, wherein the agent acts as a reversible inhibitor of human thioredoxin (page 435, 1st column, *TR assay*, page 436, 1st column, 1st full paragraph and Title). With regards to the thioredoxin inhibitor, the reference teaches that the thioredoxin inhibitors are alkyl 2-imidazole disulfide analogues, such as 1-methylpropyl-2-imidazolyl disulfide (Title and page 435, 1st column, *Chemicals* and Fig. 1). Moreover, the reference teaches that the alkyl 2-imidazolyl disulfide analogues are useful at inhibiting cellular proliferation, e.g. cell growth (page 437, Fig. 4A,B and 2nd column, last paragraph). Thus, while Oblong et al. do not explicitly teach that the agent is useful in reducing or eliminating thioredoxin-associated apoptosis inhibition, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982). Secondly, although Oblong et al. does not explicitly teach that DMSO is an acceptable carrier for intravenous administration, the claimed limitation does not appear to result in a manipulative difference when compared to the prior arts disclosure because as evidenced by Chaplan et al., DMSO is an example of an acceptable carrier for intravenous administration (Example 1, lines 27-28). Similarly, although Oblong et al. does not explicitly teach that DMSO is an acceptable carrier for oral administration, the claimed limitation does not appear to result in a manipulative difference when compared to the prior arts disclose because as evidenced by

Padmanaban et al., DMSO is an example of an acceptable carrier for oral administration (paragraph 0031). Thus the claimed composition appears to be the same as the prior art.

In response to this rejection, Applicants contend that a careful review of the literature demonstrates that one of ordinary skill in the art would not understand that DMSO could be considered a suitable carrier for injection or oral administration as evidenced by the Merck Index, Material Safety Data Sheet and several peer reviewed articles (attached as Exhibit A)), which teach that exposure to DMSO causes adverse effects in human subjects, and thus, DMSO is not considered a "pharmaceutically acceptable carrier". In addition, Applicants contend that Oblong fails to disclose a drug comprising a 2-imidazoyl disulfide and a pharmaceutically acceptable carrier for either injection or oral administration that is formulated in a suitable dosage amount for reducing or eliminating thioredoxin-associated apoptosis inhibition or thioredoxin stimulated cell growth as set forth in pending claims 7-40. Applicants further contend that there is no correlation between the in vitro dosage amount of 2-imidazolyl disulfide in DMSO and achieving a suitable dosage amount of 2-imidozolyl disulfide in other pharmaceutically acceptable carriers. Similarly, Applicants contend that Oblong does not suggest a specific appropriate in vivo dosage of 1-methylpropyl-2-imidazolyl disulfide and discloses only in vitro dosages of 1-methylpropyl-2-imidazolyl disulfide. Additionally, Applicants submit that Oblong fails to anticipate the claims because Oblong only teaches that the 2-imidazoyl disulfides inhibit the thioredoxin/thioredoxin reductase system, but does not describe the inhibition of thioredoxin as described and claimed by Applicants. In particular, Applicants assert that they unexpectedly found that select asymmetric disulfides behaved principally as inhibitors of thioredoxin rather than TR, thioredoxin reductase. Moreover, Applicants assert that they are the first to disclose appropriate dosages of 2-imidazolyl disulfides, including 1-methylpropyl-2-imidazolyl disulfide, for injection and oral administration, and the first to demonstrate the therapeutic effects of such dosages in vivo.

These arguments have been carefully considered, but are not found persuasive.

First, regarding Applicants assertions pertaining to DMSO and the submission of Exhibit A, the Examiner has carefully considered Applicants arguments as well as the material present in Exhibit A. However, while the references discuss the adverse effects of DMSO exposure, the Examiner recognizes that the references do not appear to explicitly teach that DMSO is not a pharmaceutically acceptable carrier for injection or oral administration. As such, as evidenced by

Chaplan et al. (US 5,849,737, 1998) and) and Padmanaban (US 20070105945, 2007), DMSO is a suitable carrier for injection or oral administration. Moreover, the Examiner notes that Applicants appear to be arguing that the one of ordinary skill in the art would not recognize DMSO as a pharmaceutically acceptable carrier for humans. However, it is important to point out that this limitation, e.g., human, is not claimed. Secondly, regarding Applicants assertions pertaining to Oblong et al. dosing, the Examiner acknowledges Applicants assertions that the instant claims encompass a drug comprising a 2-imidazoyl disulfide and a pharmaceutically acceptable carrier for either injection or oral administration that is formulated in a suitable dosage amount for reducing or eliminating thioredoxin-associated apoptosis inhibition or thioredoxin stimulated cell growth; and further, Oblong et al. discloses an in vitro assay. However, the Examiner recognizes that Oblong et al. teach a 10 mM solution comprising the claimed compound, e.g., 1-methylpropyl-imidazolyl disulfide, in DMSO, e.g., a pharmaceutically acceptable carrier. Thus, while the reference does not explicitly teach that a 10 mM solution is a suitable dosage amount for reducing or eliminating thioredoxin-assocaited apoptosis or thioredoxin stimulated cell growth, the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Thirdly, with regards to Applicants assertions that Oblong et al. teaches that the compounds inhibit the "system", the Examiner acknowledges Applicants contention that they unexpectedly found that select asymmetric disulfides behaved principally as inhibitors of thioredoxin rather than TR, thioredoxin reductase. However, the Examiner recognizes that Oblong et al. teaches a pharmaceutical composition which comprises the claimed 1-methylpropyl-imidazolyl disulfide, in DMSO; and therefore, the prior arts composition would inherently function the same as the claimed product. As such, granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oblong et al. (Cancer Chemotherapy and Pharmacology 1994; 34: 434-438, *IDS*) as evidenced by Chaplan et al. (US 5,849,737, 1998) and) and Padmanaban (US 20070105945, 2007).

Oblong et al. teach a composition comprising an agent in DMSO, wherein the agent acts as a reversible inhibitor of human thioredoxin (page 435, 1st column, *TR assay*, page 436, 1st column, 1st full paragraph and Title). With regards to the thioredoxin inhibitor, the reference teaches that the thioredoxin inhibitors are alkyl 2-imidazole disulfide analogues, such as 1-methylpropyl-2-imidazolyl disulfide (Title and page 435, 1st column, *Chemicals* and Fig. 1). Moreover, the reference teaches that the alkyl 2-imidazolyl disulfide analogues are useful at inhibiting cellular proliferation, e.g. cell growth (page 437, Fig. 4A,B and 2od column, last paragraph). Thus, while Oblong et al. do not explicitly teach that the agent is useful in reducing or eliminating thioredoxin-associated apoptosis inhibition, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982). Secondly, although Oblong et al. does not explicitly teach that DMSO is an acceptable carrier for intravenous administration, the claimed limitation does not appear to result in a manipulative difference when compared to the prior arts disclosure because as evidenced by Chaplan et al., DMSO is an example of an acceptable carrier for intravenous administration (Example 1, lines 27-28). Similarly, although Oblong et al. does not explicitly teach that DMSO is an acceptable carrier for oral administration, the claimed limitation does not appear to result in a manipulative difference when compared to the prior arts disclose because as evidenced by

Padmanaban et al., DMSO is an example of an acceptable carrier for oral administration (paragraph 0031). Thus the claimed composition appears to be the same as the prior art.

Oblong et al. do not teach that the amount of 1-methylpropyl-2-imidazole disulfide is 15-45 mg/m^2 or 250 mg/kg.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the dosage of 1-methylpropyl-2-imidazole disulfide as taught by Oblong et al. One would have been motivated to do so because optimization of effective amounts of known agents to be administered is considered will in the competence level of an ordinary skilled artisan in the pharmaceutical sciences, involving merely routine skill in the art. Moreover, it has been held that that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect (See In re Boesch, 205, USPQ).

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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